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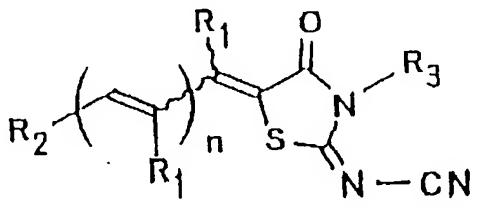
(54) 54-substituted alkylidene 2-(N-cyanoimino)-thiazolidin-4-one derivatives, their preparation and their use as aldose reductase inhibitors

(57) A class of compounds represented by the formula (I)



(I)

wherein R_1s are the same or different groups and each represents hydrogen atom or alkyl group having 1 to 4 carbon atoms; R_2 is phenyl group, naphthyl group, or either phenyl or naphthyl substituted with at least one hydroxyl, alkyl having 1 to 4 carbon atoms or alkoxy having 1 to 4 carbon atoms; R_3 is hydrogen atom, alkyl group having 1 to 4 carbon atoms or CH_2COOR_4 group, in which R_4 is hydrogen atom or alkyl group having 1 to 12 carbon atoms; n is 0 or 1, the configuration of 5-methylene group includes both E-isomer and Z-isomer, providing excepting the case wherein R_1 is hydrogen atom, R_2 is 3,5-di-t-butyl-4-hydroxyphenyl, R_3 is hydrogen atom and n is 0 or pharmacologically acceptable salts thereof when R_3 or R_4 is hydrogen atom.

The invention also concerns preparation methods thereof. The present compounds are useful as prophylactic or therapeutic agents for neuropathy, retinopathy, diabetic cataract, impediment in the kidney as tubulo-nephrosis, all known as complications of chronic diabetes and especially aldose reducing enzyme induced complications.

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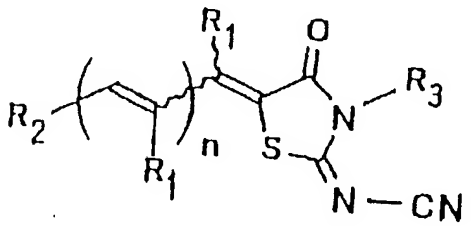
Description

Field of invention

This invention relates to a class of novel compounds, 2-(N-cyanoimino)-thiazolidin-4-one derivatives ,represented by the formula (I)



(I)

(wherein R_1s are the same or different groups and each represents hydrogen atom or C_1 -C_4 alkyl group; R_2 is phenyl group, naphthyl group or either phenyl or naphthyl group substituted with at least one hydroxyl, alkyl having 1 to 4 carbon atoms or alkoxy having 1 to 4 carbon atoms; R_3 is hydrogen atom, alkyl group having 1 to 4 carbon atoms or CH_2COOR_4 (in which R_4 represents hydrogen atom or alkyl having 1 to 12 carbon atoms); n is 0 or 1; and the configuration of 5-methylene group includes both E-isomer and Z-isomer; providing excepting the case wherein R_1 is hydrogen atom, R_2 is 3,5-di-t-butyl-4-hydroxyphenyl, R_3 is hydrogen atom and n is 0) or pharmacologically acceptable salts of the acidic form of said derivsatives when R_3 or R_4 is hydrogen atom.

Examples of alkyl group having 1 to 4 carbon atoms are methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl and the like and exsamples of said salts are sodium, potassium, ammonium salt and the like.

Background of the invention

Various compounds have been proposed for the treatment of diabetes caused by the increase in blood sugar levels which is directly connected with the poor secretion of insuline from the pancreas (hypoglycemic drug).

However, fully satisfiable compounds as medicin for the prophylaxis or treatment of complications of chronic diabetes and inter alia, aldose reducing enzyme induced complications, as ,for example, retinopathy, diabetic cataract, neuropathy, atheromic arteriosclerosis and impediment in the kidney or the like, have not been found yet.

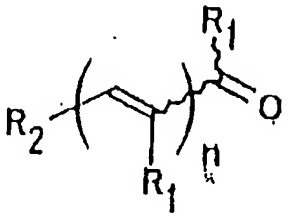
Aldose reducing enzyme is an enzyme being capable of reducing an aldose of human or other animal origins, as, for example, glucose or galactose, to the corresponding polyol as, for example, sorbitol or galactitol. When the sorbitol or galactitol thus produced by the action of this enzyme is accumulated into the lenticular, peripheral nerve, kidney or the like of the diabetes or galactosemia patients, there often causes the abovementioned complications (Biochim. Biophys. Acta 15, 8472 (1968); Jap. J. Ophthalmol. 20, 399 (1976); Int. Congr. Ser. Excerpta. Mep. 403, 594 (1944) and Metabolism 28, 456 (1979)).

The present inventors had been working for years on the subject of finding out an effective prophylactic or therapeutic agent for the abovementioned complications of the chronic diabetes, through the impediment of aldose reducing enzyme action. As the result of such studies, the inventors have found a novel class of compounds represented by the formula (I), i.e. 2-(N-cyanoimino)-thiazolidin-4-one derivatives , having an excellent aldose reducing enzyme inhibiting action and succeeded in coming to the invention.

Incidentally, in J. Med. Chem. 37,322 (1994), there describes 3,5-di-t-butyl-4-hydroxybenzylidene derivative having a similar consturuction with those of the present members and however, they indeed have 5-lipoxygenase and cycloxygenase inhibiting actions, but no aldose reducing enzyme inhibiting action.

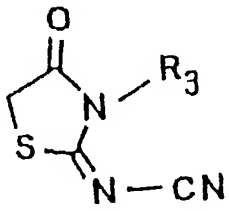
The present compounds of the formula (I) are novel compounds and they have first been prepared and examined by the inventors.

These compounds may be prepared by the reaction of an aldehyde or ketone compound represented by the formula (III)



(III)

(wherein R_1,R_2 and n are as defined hereinbefore)
with a 2-(N-cyanoimino) thiazolidin-4-one of the formula (II)



(II)

(in which R_3 is as defined hereinbefore)
in an appropriate solvent as ethanol, acetonitrile, dioxane, dimethyl formamide, dimethyl sulfoxide, pyridine, toluene, xylene and the like, or without using a solvent, and in the presence of ammonium acetate, at a temperature from room temperature to 200°C, preferably 70-150°C, for 10min. to 10 hours, usually 20min. to 5 hours, under stirring.

Preferably, an excess amount (1.1 to 5 equivalents) of aldehyde or ketone (III) is used as compared with the compound (II).

The compound (I) wherein R_3 is CH_2COOR_4 (in which R_4 has the same meaning as defined hereinbefore) may also be prepared by reacting the corresponding R_3=H compound in the presence of an alkali or its salt with a halogenized acetic acid or its ester. Examples of said alkali are metal alkali as sodium, potassium or lithium alkali and examples of said slats are sodium, potassium, ammonium salts and the like. There are geometric isomers for the present compounds and however, they are mutually transformable each other in solution by the action of light or heat.

Thus obtained compounds and their salts have an activity for inhibiting the action of aldose reducing enzyme which reduce aldose to the corresponding polyol. This means that the present compounds are useful as prophylactic or therapeutic agent for the patients suffering from neuropathy as neuralgia, retinopathy, diabetic cataract, impediment in kidney as tubulo-nephrosis, which are all kown as complications specifically connected with the aldose reducing enzyme, among the complications of chronic diabetes as, for example, circulatory disease, impediment in kidney, retinopathy, diabetic cataract, neuropathy, infectious disease and the like.

The invention shall be now more fully explained in the following Examples, which ,however, should not be taken as being limitative in any sense to the present invention.

Example 1

2-(N-cyanoimino)-5-(2-methyl-3-phenyl propenylidene) thiazolidin-4-one

A mixture of 1.41 g (0.010 mol) of 2-(N-cyanoimino) thiazolidin-4-one, 1.61 g(0.011 mol, 1.1 euqivalent) of alpha-methyl cinnamaldehyde, 0.85 g (0.011 mol, 1.1 equivalent) of ammonium acetate and 30 ml of ethanol was refluxed for 3 hours. After cooling, the mixture was added with ether and the precipitated ammonium salt was suspended in 15 ml of acetone and the suspension was added with 2 ml of conc. hydrogene chloride and 50 ml of water. The precipitated product was filtered .

2.03 g (0.0075 mol) of the objective compound were obtained as yellow needle crystals (yield 75%).
melting point: 202-203.5 °C (decomp.) (ethanol-DMF)
Mass spectrography 269(M^+), 254, 201, 174, 169, 141, 115
IR ; 3050, 2920, 2760, 2190, 1725, 1590, 1350, 1335, 1310, 1240, 1180 (KBr cm^{-1})

NMR δ = 2.21 (3H, s , CH_3) 7.34(1H, s, Ph-CH=C) 7.47 (5H, s, aromatic-H) 7.63 (1H, s, CH=C-C=O) (DMSO-d6: ppm)

Elementary analysis: as $C_{14}H_{11}N_3OS$ = 269.322			
Calc.	H 4.12%,	C 62.44%,	N 15.60%
Found	H 4.26%,	C 62.57%,	N 15.82%

Example 2

2-(N-cyanoimino)-5-(2-methyl-3-phenyl propenylidene)-4-oxo-3-thiazolidine acetic acid

A mixture of 1.50 g (0.0049mol) of potassium salt of 2-(N-cyanoimino)-5-(2-methyl-3-phenyl propenylidene) thiazolidin-4-one, 0.46 g (0.0049mol) of monochloro acetic acid, 0.81 g (0.049 mol) of potassium iodide and 10 ml of DMF was heated in an oil bath maintained at 60-70°C for 1.5 hours. After adding with water, the oily precipitate was separated and purified by means of silica gel chromatography (eluting solvent: hexane: chloroform 3:1) to obtain 0.94 g (0.0029mol) of the objective compound. Yield 59 % , as pale yellow crystals
melting point: 174-175.5 °C (decomp.) (ethyl acetate-ethanol)
Mass spectrography 327(M^+), 284, 201, 198, 173, 169, 141, 129, 115
IR ; 3300-2250, 2180, 1725, 1570, 1400, 1380, 1325, 1250, 1180, 1100, 740, 695 (KBr cm^{-1})
NMR δ = 2.27 (3H, s , CH_3) 4.54(2H, s, N-CH_2) 7.36 (1H, s, Ph-CH=C), 7.49 (5H, s aromatic-H) 7.85 (1H, s, CH=C-C=O) (DMSO-d6: ppm)

Elementary analysis: as $C_{16}H_{13}N_3O_3S$ = 327.358			
Calc.	H 4.00%,	C 58.71%,	N 12.84%
Found	H 4.31%,	C 58.53%,	N 12.73%

Example 3

2-(N-cyanoimino)-3-methyl-5-(2-methyl-3-phenylpropenylidene) thiazolidin-4-one

A mixture of 2.30 g (0.0080 mol) of ammonium salt of 2-(N-cyanoimino)-5-(2-methyl-3-phenylpropenylidene) thiazolidin-4-one , 0.50 ml (0.0080 mol) of methyl iodide and 20 ml of DMF was stirred at room temperature for overnight. After DMF was evaporated, the residue was added with water to precipitate the product. 2.20 g (0.0078 mol) of the objective compound were obtained as pale yellow needle crystals. Yield 97%
melting point: 225-226 °C (decomp.) (ethanol- DMF)
Mass spectrography 283(M^+), 268, 201, 198, 174, 169, 141, 129, 115
IR ; 2200, 1705, 1580, 1430, 1375, 1300, 1125, 765,735, 700 (KBr cm^{-1})
NMR δ = 2.32 (3H, s , CH_3) 3.31(3H, s, N-CH_3) 7.33-7.60 (6H, m, Ph-CH=C,aromatic-H) 7.80 (1H, s, CH=C-C=0) (DMF-d7: ppm)

Elementary analysis: as $C_{15}H_{13}N_3OS$ = 283.349			
Calc.	H 4.62%,	C 63.58%,	N 14.83%
Found	H 4.87%,	C 63.69%,	N 14.84%

Example 4

2-(N-cyanoimino)-5-(3,4-methylenedioxybenzylidene) thiazolidin-4-one

Using the same method as stated in Example 1, 2-(N-cyanoimino)-5-(3,4-methylenedioxybenzylidene) thiazolidin-4-one was prepared from 2-(N-cyanoimino)thiazolidin-4-one and piperonal.
Yield 89% ; yellow crystals
melting point: 272°C (decomp.) (ethanol- DMF)
Mass spectrography 273(M⁺), 178, 148, 120, 94
IR ; 3070,2920,2760, 2190, 1720, 1580, 1495, 1485, 1445, 1360, 1270, 1230, 1180, 1100, 1035 , 920, 485 (KBr cm^{-1})
NMR δ = 6.17 (2H, s ,O-C$\underline{H}_2$-O) 6.95-7.35 (3H, m, 2'-,5'-,6'-H) 7.81 (1H, s, C$\underline{H}$=C-C=O) (DMSO-d6: ppm)

Elementary analysis: as $C_{12}H_7N_3O_3S$ = 273.266			
Calc.	H 2.58%,	C 52.74%,	N 15.38%
Found	H 2.55%,	C 52.98%,	N 15.34%

Example 5

2-(N-cyanoimino)-5-(2-naphthylmethylene) thiazolidin-4-one

Using the same method as stated in Example 1, 2-(N-cyanoimino)-5-(2-naphthylmethylene) thiazolidin-4-one was prepared from 2-(N-cyanoimino)thiazolidin-4-one and 2-naphthaldehyde.
Yield 66% ; pale yellow crystals
melting point: 243°C (decomp.) (ethanol- DMF)
Mass spectrography 279(M⁺), 184, 152, 139
IR ; 3070,2930,2760, 2190, 1720, 1600, 1580, 1480, 1360, 1340, 1330,1300, 1270, 1230, 1210, 1175 ,805, 740, 730, 470 (KBr cm^{-1})
NMR δ = 7.45- 7.87 (3H, m, 3'-,6'-, 7'-H), 7.87-8.35 (5H,m, 1'-,4'-, 5'-,8'-H, C$\underline{H}$=C-C=O) (DMSO-d6: ppm)

Elementary analysis: as $C_{15}H_9N_3OS$ = 279.317			
Calc.	H 3.25%,	C 64.50%,	N 15.04%
Found	H 3.11%,	C 64.47%,	N 14.91%

Example 6

5-benzylidene-2-(N-cyanoimino)-4-oxythiazolidine

Using the same method as stated in Example 1, 5-benzylidene-2-(N-cyanoimino)-thiazolidin-4-one was prepared from 2-(N-cyanoimino) thiazolidin-4-one and benzaldehyde.
Yield 85%; pale yellow crystals
melting point: 226°C (decomp.) (ethanol- DMF)
Mass spectrography 229(M⁺), 134, 90
IR ; 3030,2920,2760, 2220, 1725, 1605, 1490, 1445, 1350, 1290, 1240,1190, 1180, 525 (KBr cm^{-1})

NMR δ = 7.45- 7.80 (5H, m, aromatic-H), 7.88(1H,s,CH=C-C=O) (DMSO-d6: ppm)

Elementary analysis: as $C_{11}H_7N_3OS$ = 229.257			
Calc.	H 3.32%,	C 57.72%,	N 18.19%
Found	H 3.08%,	C 57.63%,	N 18.33%

Example 7

2-(N-cyanoimino)-5-(3-phenylpropenylidene) thiazolidin-4-one

Using the same method as stated in Example 1, 2-(N-cyanoimino)-5-(3-phenylpropenylidene) thiazolidin-4-one was prepared from 2-(N-cyanoimino)thiazolidin-4-one and trans-cinnamaldehyde.
Yield 69%; pale yellow crystals
melting point: 250°C (decomp.) (ethanol- DMF)
Mass spectrography 255(M^+), 160, 155, 134, 128, 115
IR ; 3025,2940,2750, 2190, 1720, 1595, 1480, 1445, 1400, 1350, 1330,1320, 1260, 1185, 1150, 980, 960, 815, 755, 715 (KBr cm^{-1})
NMR δ = 6.89- 7.97 (8H, m, CH=CH-CH=C-C=O aromatic-H), (DMSO-d6: ppm)

Elementary analysis: as $C_{13}H_9N_3OS$ = 255.295			
Calc.	H 3.55%,	C 61.06%,	N 16.46%
Found	H 3.40%,	C 61.22%,	N 16.34%

Example 8

2-(N-cyanoimino)-5-[2-(6-methoxynaphthyl)methylene] thiazolidin-4-one

Using the same method as stated in Example 1,2-(N-cyanoimino)-5-[2-(6-methoxynaphthyl)methylene] thiazolidin-4-one was prepared from 2-(N-cyanoimino) thiazolidin-4-one and 6-methoxy- naphtho aldehyde.
Yield 91%; yellow crystals
melting point: 256°C (decomp.) (ethanol- DMF)
Mass spectrography 309(M^+), 214, 199, 171, 141
IR ; 3050,2920,2750, 2190, 1720, 1585, 1490, 1480, 1390, 1350, 1330,1300, 1270, 1195, 1170, 1035,860, 840, 800, 710 (KBr cm^{-1})
NMR δ = 3.94 (3H, s, O-CH_3) 7.25-8.33 (6H, m, aromatic-H), 7.98 (1H, s, CH=C-C=O)(DMSO-d6: ppm)

Elementary analysis: as $C_{16}H_{11}N_3O_2S$ = 309.343			
Calc.	H 3.58%,	C 62.12%,	N 13.58%
Found	H 3.53%,	C 61.89%,	N 13.69%

Example 9

2-(N-cyanoimino)-5-(1-naphthylmethylene) thiazolidin-4-one

A mixture of 1.79 g (0.010 mol) of potassium salt of 2-(N-cyanoimino) thiazolidin-4-one, 1.72 g (0.011 mol, 1.1 equivalent) of alpha-naphthoaldehyde, 0.85 g (0.011 mol, 1.1 equivalent) of ammonium acetate and 30 ml of ethanol was refluxed for 2 hours.After cooling, the mixture was added with ether to precipitate the potassium salt , which was separated and again suspended in 15 ml of acetone. 2ml of conc. HCl and 50 ml of water were added to the suspension, and the precipitated crystals were filtered to obtain 2.32 g (0.0083 mol) of the objective compound as yellow crystals. Yield 83%.
Melting point: 230°C (decomp.) (ethanol- DMF)
Mass spectrography 279(M+), 184, 179, 152, 139
IR ; 3120,3030,2940,2770, 2190, 1705, 1600, 1585, 1350, 1215, 795, 770, 720, 550 (KBr cm^{-1})
NMR δ = 7.50-7.90 (4H, m, 2'-,3'-,6'-,7'-H) 7.90-8.35 (3H, m, 4'-,5'-,8'-H) 8.54 (1H, s,CH=C-C=O) (DMSO-d6:ppm)

Elementary analysis: as $C_{15}H_9N_3OS$ = 279.317			
Calc.	H 3.25%,	C 64.50%,	N 15.04%
Found	H 3.64%,	C 64.73%,	N 15.16%

Example 10

2-(N-cyanoimino)-5-(4-hydroxy-3-methoxybenzylidene) thiazolidin-4-one

Using the same method as stated in Example 9, 2-(N-cyanoimino)-5-(4-hydroxy-3-methoxybenzylidene) thiazolidin4-one was prepared from potassium salt of 2-(N-cyanoimino) thiazolidin-4-one and vaniline .
Yield 91% :yellow orange crystal
Melting point: 238°C (decomp.) (ethanol- DMF)
Mass spectrography 275(M+), 180, 165, 137, 109
IR ; 3330,3030,2920,2760, 2190, 1720(sh), 1695, 1575, 1505,1370, 1350, 1295, 1220, 1180, 1125, 1020, 810, 720, 620, 530, 480 (KBr cm^{-1})
NMR δ = 3.87 (3H, s, O-CH_3) 6.80-7.35 (3H, m, aromatic-H), 7.82 (1H, s,CH=C-C=O) (DMSO-d6:ppm)

Elementary analysis: as $C_{12}H_9N_3O_3S$ = 275.282			
Calc.	H 3.30%,	C 52.36%,	N 15.26%
Found	H 3.52%,	C 52.41%,	N 15.19%

Example 11

2-(N-cyanoimino)-5-(3-methylbenzylidene) thiazolidin-4-one

Using the same method as stated in Example 9, 2-(N-cyanoimino)-5-(3-methylbenzylidene) thiazolidin-4-one was prepared from potassium salt of 2-(N-cyanoimino) thiazolidin-4-one and m-tolualdehyde .
Yield 90% :pale yellow crystal
Melting point: 214-214.5°C (decomp.) (ethanol- DMF)
Mass spectrography 243(M+), 148, 115
IR ; 3040,2940,2760, 2190, 1730, 1610, 1580, 1350,1295,1255, 1215, 1160, 780, 720, 540, 520, (KBr cm^{-1})

NMR δ = 2.40 (3H, s, CH_3) 7.45 (4H, s, aromatic-H), 7.84 (1H, s,CH=C-C=O) (DMSO-d6:ppm)

Elementary analysis: as $C_{12}H_9N_3OS$ = 243.284			
Calc.	H 3.73%,	C 59.24%,	N 17.27%
Found	H 4.07%,	C 59.73%,	N 17.49%

Example 12

2-(N-cyanoimino)-5-[3-(2- methoxyphenyl) propenylidene] thiazolidin-4-one

Using the same method as stated in Example 9, 2-(N-cyanoimino)-5-[3-(2- methoxyphenyl) propenylidene] thiazolidin-4-one was prepared from potassium salt of 2-(N-cyanoimino) thiazolidin-4-one and 2-methoxy cinnamaldehyde.
Yield 80% :yellow orange needle crystal
Melting point: 220°C (decomp.) (ethanol- DMF)
Mass spectrography 285(M^+), 201, 190, 185, 175, 147, 131, 115IR ; 3160,3070, 2930,2750, 2180, 1720, 1580, 1480,1320,1240,1150, 1010, 980, 750, 720 (KBr cm^{-1})
NMR δ = 3.90 (3H, s, O-CH_3) 6.80-8.00 (7H, m, CH=CH-CH=C-C=O, aromatic-H) (DMSO-d6:ppm)

Elementary analysis: as $C_{14}H_{11}N_3O_2S$ = 285.321			
Calc.	H 3.89%,	C 58.94%,	N 14.73%
Found	H 4.14%,	C 59.09%,	N 14.64%

Example 13

2-(N-cyanoimino)-5-(1-phenylethylidene) thiazolidin-4-one potassium salt

A mixture of 1.41 g (0.010 mol) of 2-(N-cyanoimino) thiazolidin-4-one, 1.80 g(0.015 mol, 1.5 equivalent) of acetophenone,and 0.15 g (0.0020 mol) of ammonium acetate was heated in an oil bath maintained at 110-120°C for 20 minutes. After cooling, the mixture was added with 2N HCl and chloroform and an organic layer was separated. Thus obtained organic phase was washed with water, dried and solvent was removed off to obtain the crude product, which was then purified by means of silica gel column chromatography (eluting solvent: hexane-chloroform 3:2).

The purified product was dissolved in ethanol and added with an equivalent amount of potassium hydroxide and stirred well.

Thereafter, ethanol solvent was removed off to obtain the objective potassium salt, which was then recrystallized from isopropanol to obtain the purified product as pale orange crystals.
Melting point: 273-274°C (decomp.) (isopropanol)
IR ; 2170,1650, 1580, 1480, 1320, 1290, 1250, 770, 755, 690, 560 (KBr cm^{-1})
NMR δ = 2.64 (3H, s, CH_3) 7.45 (5H, s, aromatic-H) (DMSO-d6:ppm)

Example 14

2-(N-cyanoimino)-5-(1-phenylpropylidene) thiazolidin-4-one

A mixture of 2.82 g (0.020 mol) of 2-(N-cyanoimino) thiazolidin-4-one, 5.36 g (0.040 mol, 2 equivalent) of propiophenone and 1.70 g (0.022 mol) of ammonium acetate was heated in a bath maintained at 130-140°C for 25 minutes. After cooling, the mixture was added with 2N NaOH and ether and mixed well. The aqueous phase was separated , acidified with conc. HCl and extracted with chloroform. The chloroform extract was then washed with water, dried and the solvent was removed off to obtain the crude product. The crude product was thereafter subjected to silica gel column chromatography (eluting solvent :hexane-chloroform 3:2) to obtain 1.52 g (0.0059 mole) of the objective compound .

Yield : 30% as pale yellow crystals
Melting point: 191-192°C (decomp.) (ethyl acetate-hexane)
Mass spectrography 257(M+), 190, 162, 157, 147, 129, 103
IR ;3030, 2920,2760, 2180, 1710, 1590, 1480,1330,1210,1035, 770, 695, 550 (KBr cm^{-1})
NMR δ = 0.98 (3H, t, J=7.5Hz $C\underline{H}_3$) 3.25 (2H, q, J=7.5Hz, $C\underline{H}_2$) 7.45 (5H,s, aromatic-H) (DMSO-d6:ppm)

Elementary analysis: as $C_{13}H_{11}N_3OS$ = 257.311			
Calc.	H 4.31%,	C 60.68%,	N 16.33%
Found	H 4.49%,	C 60.44%,	N 16.10%

Example 15

2-(N-cyanoimino)-5-[1-(2-naphthyl)ethylidene] thiazolidin-4-one

A mixture of 1.41g (0.010mol) of 2-(N-cyanoimino) thiazolidin-4-one ,2.55 g (0.015 mol, 1.5 equivalent) of acetonaphthone and 0.15 g (0.0020 mol) of ammonium acetate was heated in an oil bath maintained at 120-125°C for 20 minutes. After cooling, the mixture was added with 2N HCl and chloroform and an organic phase was separated, washed with water, dried and distilled the solvent off. Thus obtained crude product was purified by means of silica gel column chromatography (eluting solvent: hexane-chloroform 3:2) to obtain 1.76 g (0.0060 mol) of the purified objective compound.
Yield : 60% as pale yellow crystals
Melting point: 191-191.5°C (decomp.) (ethyl acetate-hexane)
Mass spectrography 293(M+), 198, 165, 128
IR ;3120, 3050,2940, 2770, 2180, 1720(sh), 1700,1580, 1330,1230,1025, 825, 750, 720, 635, 540, 480 (KBr cm^{-1})
NMR δ = 2.81 (3H, s, $C\underline{H}_3$) 7.50-7.85 (3H, m, 3'-, 6'-, 7'-H) 7.85-8.25 (4H, m, 1'-, 4'-, 5'-, 8'-H) (DMSO-d6:ppm)

Elementary analysis: as $C_{16}H_{11}N_3OS$ = 293.344			
Calc.	H 3.78%,	C 65.51%,	N 14.33%
Found	H 4.02%,	C 65.39%,	N 13.89%

Effect of the invention

Aldose reducing enzyme inhibiting activity of the respective 2-(N-cyanoimino) thiazolidin-4-one derivatives was measured according to the method by Hayman et al (J. Biol. Chem., 240 877 (1965)) The employed aldose reducing enzyme was Human, Recombinant.

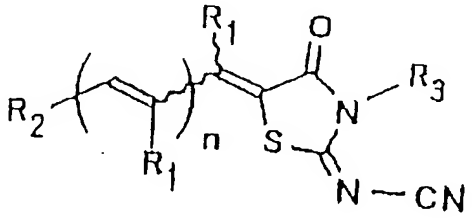
The following table shows "inhibition rate (%)" which means the inhibiting activity at the 1.0×10^{-7} mol concentration level of the tested compound .

Table 1

Example No.	Inhibition rate (%)
1	72
2	100
3	12
4	44
5	44
6	32
7	44
8	68
9	20
10	100
11	52
12	84
13	60
14	12
15	64

Claims

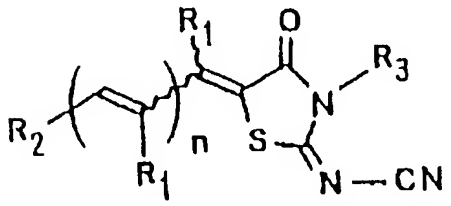
1. 2(N-cyanoimino)-thiazolidin-4-one derivatives of the formula(I):



(I)

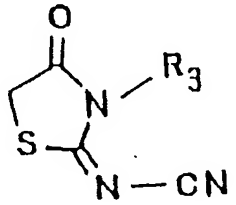
(wherein R_1 s are the same or different groups and each represents hydrogen atom or alkyl group having 1 to 4 carbon atoms; R_2 is phenyl group, naphthyl group or either phenyl or naphthyl substituted with at least one hydroxyl, alkyl having 1 to 4 carbon atoms or alkoxy having 1 to 4 carbon atoms; R_3 is hydrogen atom, alkyl group having 1 to 4 carbon atoms or CH_2COOR_4 group (in which R_4 is hydrogen atom or alkyl having 1 to 12 carbon atoms); n is 0 or 1 and the configuration of 5-methylene group includes both E-isomer and Z-isomer, providing excepting the case wherein R_1 is hydrogen atom, R_2 is 3,5-di-t-butyl-4-hydroxyphenyl, R_3 is hydrogen atom and n is 0) or pharmacologically acceptable salts of the acidic form of said derivatives when R_3 or R_4 is hydrogen atom.

2. A process for preparing a 2-(N-cyanoimino)-thiazolidin-4-one derivative represented by the formula (I)



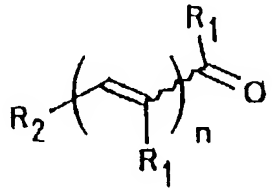
(I)

(wherein R_1, R_2, n and R_3 are as defined hereinunder) or salts thereof, which is characterized by that a 2-(N-cyanoimino)-thiazolidin-4-one derivative of the formula (II)



(II)

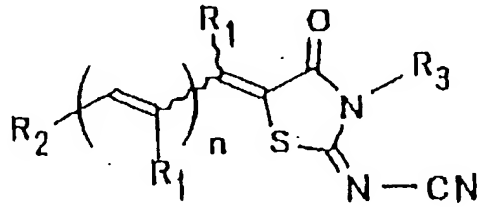
(in which R_3 is hydrogen atom, alkyl group having 1 to 4 carbon atoms or CH_2COOR_4 group, and R_4 is hydrogen atom or alkyl group having 1 to 12 carbon atoms) or its salt
is reacted with an aldehyde or ketone compound of the formula (III)



(III)

(in which R_1 s are the same or different groups and each represents hydrogen atom or alkyl group having 1 to 4 carbon atoms; R_2 is phenyl group, naphthyl group ,or either phenyl or naphthyl substituted with at least one hydroxyl, alkyl having 1 to 4 carbon atoms or alkoxy having 1 to 4 carbon atoms; n is 0 or 1; providing excepting the case wherein R_1 is hydrogen atom, R_2 is 3,5-di-t-butyl-4-hydroxyphenyl and n is 0)

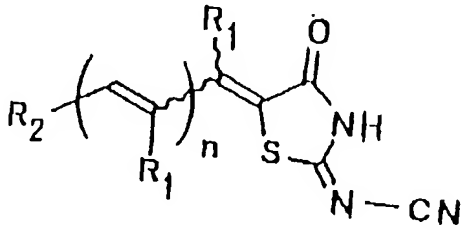
3. A process for preparing a 2-(N-cyanoimino)-thiazolidin-4-one derivative of the formula (I)



(I)

(wherein R_1, R_2, n and R_3 are as defined hereinunder)
which is characterized by that

a 2-(N-cyanoimino)-thiazolidin-4-one derivative of the formula (IV)



(IV)

(in which R_1 s are the same or different groups and each represents hydrogen atom or alkyl group having 1 to 4 carbon atoms; R_2 is phenyl group, naphthyl group,or either phenyl or naphthyl substituted with at least one hydroxyl, alkyl having 1 to 4 carbon atoms or alkoxy having 1 to 4 carbon atoms; n is 0 or 1; and the configuration of 5-methylene group includes both E-isomer and Z-isomer, providing excepting the case wherein R_1 is hydrogen atom, R_2 is 3,5-di-t-butyl-4-hydroxyphenyl and n is 0)
or its salt is reacted ,in the former case in the presence of an alkali, with a halide compound of the formula :

R_3X

(in which R_3 is alkyl group having 1 to 4 carbon atoms or CH_2COOR_4 group, and R_4 is hydrogen atom or alkyl group having 1 to 12 carbon atoms).

4. 2-(N-cyanoimino)-5-(2-methyl-3-phenyl propenylidene)-thiazolidin-4-one
5. 2-(N-cyanoimino)-5-(2-methyl-3-phenyl propenylidene)-4-oxo-3-thiazolidine acetic acid
6. 2-(N-cyanoimino)-5-[2-(6-methoxy naphthyl) methylene]-thiazolidin-4-one
7. 2-(N-cyanoimino)-5-(4-hydroxy-3-methoxy benzylidene)-thiazolidin-4-one
8. 2-(N-cyanoimino)-5-[3-(2-methoxyphenyl) propenylidene]-thiazolidin-4-one
9. 2-(N-cyanoimino)-5-(1-phenylethylidene)-thiazolidin-4-one potassium salt
10. 2-(N-cyanoimino)-5-[1-(2-naphthyl) ethylidene]-thiazolidin4-one

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 30 4416

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	EP-A-0 449 216 (WARNER-LAMBERT COMPANY) 2 October 1991 * examples 9,9B,40 * ---	1-3	C07D277/54 C07D417/06 A61K31/36 A61K31/425
D,X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 2, 21 January 1994 pages 322-328, UNANGST P.C. ET AL. 'Synthesis and biological evaluation of 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]oxazoles, -thiazoles, and -imidazoles: Novel dual 5-lipoxygenase and cyclooxygenase inhibitors with antiinflammatory activity' * page 325; compound 13a * ---	1-3	
Y	EP-A-0 047 109 (ONO PHARMACEUTICAL CO., LTD.) 10 March 1982 * the whole document * ---	1,4-10	
Y	TETRAHEDRON LETTERS, vol. 30, no. 8, March 1989 pages 959-962, ISHIDA T. ET AL. 'Structural elucidation of epalrestat (ONO-2235), a potent aldose reductase inhibitor, and isomerization of its double bonds' * the whole document * ---	1,4-10	TECHNICAL FIELDS SEARCHED (Int.Cl.6) C07D A61K
	-/--		

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	9 November 1995	Hartrampf, G

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 30 4416

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y	JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 2, no. 7, July 1990 pages 1085-1091, ISHIDA T. ET AL. 'Conformation of (Z)-3-carboxymethyl-[(2E)-2-methyl-3-phenylpropenylidene]rhodanine (Epalrestat), a potent aldose reductase inhibitor: X-ray crystallographic, energy calculational, and nuclear magnetic resonance studies' * the whole document *	1,4-10	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

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